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Supportive tissue in tumors hinders, rather than helps, pancreatic cancer

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Fibrous tissue long suspected of making pancreatic cancer worse actually supports an immune attack that slows tumor progression but cannot overcome it, scientists at The University of Texas MD Anderson Cancer Center report in the journal *Cancer Cell*.

"This supportive tissue that's abundant in pancreatic cancer tumors is not a traitor as we thought but rather an ally that is fighting to the end. It's a losing battle with cancer cells, but progression is much faster without their constant resistance," said study senior author Raghu Kalluri, Ph.D., M.D., chair of Cancer Biology. "It's like having a car with weak yet functioning brakes vs. having one with no brakes."

The team's findings point to a potential new avenue for guiding treatment, including immunotherapy, and offer an explanation for the failure of a promising combination drug approach in clinical trials.

"Cancer is one form of tissue injury. When our defense system detects damaged cells it sends soldiers to contain and repair the damage," Kalluri said. "When it cannot remove the damaged cells and repair the injured area, our defensive fibrotic response tries to put a boundary around it, to contain it and prevent it from spreading."

Pancreatic cancer is resistant to treatment and only about 7 percent of patients survive for five years. An estimated 46,420 new U.S. cases will be diagnosed in 2014 and 39,590 people will die of the disease.

Study results consistent with failed clinical trial

Kalluri and colleagues used genetically engineered mouse models that allowed depletion of tissue-repair cells called myofibroblasts in pancreatic cancer. Myofibroblasts compose a major portion of supportive tissue called stroma and also produce collagen, which serves as a scaffold for wound-healing and tissue regeneration. Up to 90 percent of a pancreatic tumor can consist of fibrotic support tissue.

When the scientists depleted myofibroblast production in mice with either early or later-stage pancreatic ductal adenocarcinoma their tumors became much more invasive, aggressive and lethal.

"We did these experiments thinking that we would show the importance of myofibroblasts and fibrosis in pancreas cancer progression, but the results went completely against that hypothesis," Kalluri said.

Since myofibroblasts and collagen are thought to block chemotherapy, the team treated their myofibroblast-depleted mice with gemcitabine, the standard treatment for pancreas cancer. The drug did not have any effect on the disease course or improve survival.

These results track those of a major clinical trial that combined a myofibroblast-depleting drug called a hedgehog inhibitor with gemcitabine to treat pancreatic cancer patients. The trial was stopped in 2012 when an interim analysis showed the patients taking the combination had faster disease progression than the control group that took only gemcitabine, a surprising result.

"This paradigm-shifting study identifies the reason why the hedgehog-inhibitor trials failed," said co-author Anirban Maitra, M.D., professor of Pathology and scientific director of the Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research.

All solid tumors include some degree of fibrosis, Maitra said, but not as much as pancreas cancer.

The team's analysis of pancreatic tumors from 53 patients showed low levels of tumor myofibroblasts are associated with decreased survival.

Study findings are consistent with pathologic evidence that tumors with more fibrotic tissue more closely resemble normal pancreas tissue, indicating a better prognosis for patients, even though lab experiments indicated those tumors should be more aggressive, Maitra said.

"These findings also are likely to account for rather modest results in a phase I clinical trial of immunotherapy alone for pancreatic cancer," Maitra said. "But it's not just a negative study, because it suggests what might work for these patients."

And what might work hinges on immune checkpoint blockade.

The immune system connection

To understand the cause of the swift progression, the team conducted gene expression profiling and RNA sequence analysis comparing control tumors to myofibroblast-depleted tumors.

Genes associated with tumor immunity were suppressed and fewer T cells and B cells infiltrated the myofibroblast-depleted tumors. The proportion of regulatory T cells, which suppress immune response, increased. They found greater expression of the immune checkpoint CTLA-4, which shuts down immune response.

The researchers then set up a new experiment using ipilimumab, a drug developed by co-author Jim Allison, Ph.D., chair of Immunology, that blocks CTLA-4, freeing T cells to attack tumors.

Mice with depleted myofibroblasts who were treated with ipilimumab to stifle CTLA-4 had an average survival increase of 60% compared to untreated control mice and those with either depleted myofibroblasts or treated with ipilimumab alone.

These findings suggest that ipilimumab might work for patients with low levels of fibrosis in their tumors, Kalluri noted. Combining ipilimumab with a hedgehog inhibitor is likely to work better for those with high-fibrosis. The Kalluri laboratory is exploring these issues.

Provided by University of Texas M. D. Anderson Cancer Center